Thermobiology and Clinical Application of Interstitial and Superficial Hyperthermia in Two Groups of Patients

A New Approach for Treating Malignant Tumors

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ABSTRACT
Masasutie Tjokronegoro & M. H. Segenbach - Thermobiologi dan aplikasi teknik hyperthermia interstitial dan superfisial pada 2 kelompok pasien: Cara baru untuk pengobatan tumor maligna


Kelompok pertama terdiri dari 8 kasus (4 kasus karinomia adas meluket dan 5 kasus karinomia lala) dan kasus kasus secara bersama diberi dengan radiasi dan hyperthermia interstitial. Hasilnya adalah 7 kasus mengalami remisi kompleks (87.5%), sedangkan satu kasus mengalami remisi parial (12.5%).

Kelompok kedua terdiri dari 6 penderita (5 kasus karinomia mammae retak dan 1 kasus penderita carcinoma paru) diberi dengan kombinasi radiasi elektrom 12 megawatt dari pesawat Mevator 10 Siemens dan hyperthermia superficial dengan mengunakan pesawat Lund Boucher Hyperthermia System 6010, 5.5 Mhz/26 W, dengan suhu 42.5 derek. Pada 4 kasus mengalami remisi kompleks (66.6%) dan dua kasus mendapat remisi parial (33.3%).

Sehingga latar belakang hyperthermia diureka juga hasil-prinsip-prinsip thermobiologi, ins-nuklar hyperthermia dengan radiasi, mekanisme fisikologi, efek hyperthermia terhadap mikrooksilur tumor, dan prinsip dasar fisika serta instrumenasi hyperthermia.

INTRODUCTION AND HISTORICAL REVIEW

The effect of heat in malignant tumors was first reported by Hippocrates. In 1856 Buch described the disappearance of soft tissue scars following high fever in patients with erysipelas. Later Coley induced artificial fever by injecting bacterial toxin, and Westermark used localized hyperthermia to treat gynecologic cancer and produced tumor regression. Warren reported on 52 patients.

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with advanced cancer, treated with combination of heat-induced pyrogenic substances and X-ray therapy. Twenty-nine of these 34 patients showed improvement for 1 to 6 months.

In the beginning of the 1970s hyperthermia was almost abandoned for several decades due to technical problems. But in the past 20 years interest has been relkindled in the clinical application of this modality. Numerous papers have indicated that there is a significant advantage in the use of heat combined with radiation or systemic drugs to enhance the killing of tumor cells (DeBrey et al., 1979, 1977; Feld & Bleichrodt, 1979; Stewart & Derkach, 1977). Significant progress has been made in clinical thermometry by introduction of invasive thermometry sensor in subcutaneous tissue and into tumors, which provide reliable information on the heat distribution within the target areas.

The instrumentation to deliver effective heat deep seated tumors is still in progress.

There is also a strong clinical rationale for the use of hyperthermia, since about 90% to 50% of patients with solid tumor have recurrences at primary site. Many of primary treated tumors have regional lymph node recurrences. Both factors could be improved if effective radiation sensitizers are developed and applied in conjunction with radiation therapy.

**THERMOBIOLOGY OF HYPERTERMIA**

In vitro and in vivo experiments strongly suggest that heat may be more damaging to tumor tissue than normal tissue for several reasons:

1. Hypoxic cells may have an increased sensitivity to heat. The fact at least as thermotolerant as oxygenated cells (DeBrey et al., 1977).
2. Metabolically deprived tumor cells with reduced pH are more heat sensitive.
3. Heat affects cells in S phase, which are known to be resistant to radiation, and

Heat in conjunction with radiation causes a greater degree of intracellular death than radiation alone and this may affect the cell phase distribution within the cell cycle after heat or X-ray exposure. The heat sensitivity of hypoxic cells is increased by low oxygen tension, or nutrient deficiency, or reduced pH. The rapid response of tumors may be affected by physiologic changes associated with lowering of blood flow and oxygen tension produced by hyperthermia (DeBrey et al., 1977).

Biomolecular mechanisms by which heat kills or diminishes malignant cells are summarized in three major problems:

1. Cellular membrane damage with changes in permeability, composition and fluidity, ultimately leading to the death of cells (Wullach et al., 1968; Struefler et al., 1978:19-26). Heat affects on membrane fluidity have been in conjunction with the interaction of heat with membrane modifying drugs, i.e. alcohol and local anesthetics (Gary 1977). An inverse relation between cholesterol and phospholipid ratio and heat sensitivity was shown in studies with several cell lines (Cress & Germer, 1980).
2. Damage to the lysosomes of the cellular cytoplasm as suggested by Overgaard. Desintegration of lysosomes and cellular damage by the released digestive enzymes are discussed as the cause of cellular death. Biochemical evidence of increased lysosomolytic enzyme activity in heated cells was reported by Hume et al. (1978) and Overgaard & Overgaard (1972).

3. Thermal damage to protein was suggested by Tomasicov and associates (Tomasicov et al., 1978; Roti Roti & Wallward, 1978). They reported an increased, non-specific attachment of non-histone nuclear protein to DNA following heat exposure; however, this phenomenon showed only limited correlation to cell killing and is more likely an important sensitizing mechanism by preventing repair of radiation damage (Dickson & Shah, 1972). Heat produces effects on various proteins such as DNA (Dube et al., 1977; Tomasicov et al., 1978). RNA (Warchoeiker & Scheerker, 1969), and protein synthesis (Mondovi et al., 1969), and respiration (Mondovi et al., 1969). CEF cells exposed to various time of temperature ranging from 41.5°C to 46°C Care killed at an exponential rate. A marked increase in the cells sensitivity to heat exposure occurs between 40°C and 43°C.

HEAT INTERACTION WITH IRRADIATION

Combination of heat and irradiation is of potential benefit in cancer therapy. The first most generally observed phenomenon is heat radiosensitization of cells (Dewe et al., 1977; Peret et al., 1980; Suprata et al., 1979). In S phase cells are more radiosensitized by heat than are cells in G1 (Suprata et al., 1978). It is believed that accumulation of non-histone protein which binds to DNA following heat treatment prevents the cells from repairing radiation damage. This hypothesis is supported by several observations. First, the interaction between heating and subsequent radiation exposure persists for about 42 hours between subsequent heat exposures. This coincides with the return to a normal DNA to non-histone protein ratio (Clark et al., 1981). Second, the observation that inhibition of enzymatic repair of induced thymic damage occurs only when chromatins is heated, but not when only exposed to heat (Waters & Roti Roti, 1988). Third, there is a linear increase both in the amount of non-histone protein attached to DNA and in the inhibition of micrococcal nuclease digestion of chromatins in fundamental nucleosome structure, which suggests that access to the sites between nucleosomal structure is blocked (Waters et al., 1978).

Another factor of possible clinical relevance is the fact that cells in G1 are less sensitive to heat than cells in S phase, whereas S phase cells are normally resistant to radiation. The magnitude of difference between G1 and S phase is reduced if the severity of the heat exponentially decreases (Weste & Hewey, 1971).

PHYSIOLOGIC MECHANISMS OF HYPER THERMIA IN MICR Ovascula TURE OF TUMORS

1. Effect of hyperthermia on normal tissue microcirculation

The blood flow of skin overlying the tumor and muscle near the tracer is twice than blood flow in skin and muscle far from the tumor (Song et al., 1980).
It is similar to an inflammatory process near the tumor. There is a significant increase in the blood flow in skin and muscle both near and far from the tumor upon heating to 43°C for 1 hour (Song et al., 1980). The blood flow of normal tissue surrounding the tumor returned to normal levels within 2 hours after cessation of heating.

5. Role of blood flow in tumor microcirculation in combined use of hyperthermia and other modalities

These are indications that hypoxic cell fraction in a tumor increases as a result of vascular damage, despite the fact that heat induced death primarily decreases hypoxic cells. Song and coworkers found that the proportion of hypoxic cells in SCLC tumors was about 45%; it is increased to about 95% at 3 hours.
after heating to 45.5°C for 30 minutes. The proportion of hypoxic cells decreased to almost 0 after this period, probably because of cell death as well as reoxygenation of hypoxic cells, but the proportion of hypoxic cells 48 to 72 hours after heating was still greater than that in the unheated tumor. In contrast, partial hypoxic normal tissues may be better oxygenated by an increase in blood flow, causing an increase in radiosensitivity. This thermal enhancement is the strongest argument for the potential benefit of hyperthermia. These facts also strongly suggest that the therapeutic gain may be greater if radiation therapy is applied before hyperthermia rather than vice versa.

**EFFECT OF HYPERTHERMIA ON INTRATUMOR pH**

The pH of arterial blood flow is 7.4 and that of venous blood flow and interstitial fluid is about 7.35. Intracellular pH usually ranges between 6.0 and 7.4 in different cells, averaging about 7.10. Recent studies have shown that there is no significant difference between the intracellular pH of normal cell lines and that of their malignant counterparts (Jadad et al., 1982).

Hyperthermia triggers an immediate and significant decrease of the pH in tumors (Bicher et al., 1980; Song et al., 1980). The pH in SIRC-tumor of mice decreased from 7.65 to 6.67 when tumors were heated at 48.5°C for 30 minutes. When heat was terminated, the pH rose to 6.78, but decreased to 6.5 to 6.6 in tumors (Song et al., 1980). The lowering of tumor pH caused by hyperthermia is a result of an increase in the acidic metabolites. So acidic condition not only enhances heat killing but also inhibits repair of thermal damage (Song et al., 1980), and development of thermotolerance (Goldin & Leeper, 1981; Overgaard et al., 1979).

The reason for decreased pH in tumors is an increase of lactic acid contents in mouse tumor, as well as pyruvate and pyruvic acid (Streffer et al., 1981).

**BASIC PRINCIPLES OF PHYSICS AND INSTRUMENTATION**

Instrumentation in clinical hyperthermia is concentrated in three major problems: 1. power deposition
   1.1. thermometry
   1.2. treatment planning
   1.3. safety.

1. Power deposition

The physical agents employed for power deposition in local clinical hyperthermia are:

- Electromagnetic irradiation at very high and microwave frequencies (300 to 2450 Megahertz).
- Electric and magnetic fields at radio frequencies (0.1 to 27 Megahertz) and ultrasound waves with frequency ranging from 0.3 to 3 Megahertz.

The temperature versus time plot during the very first stage of heating is a typically straight line. During this early time interval (typically 20 to 30 seconds) the constant rate of temperature rise is directly proportional to the absorbed power.
density (Watts/cm²) at the point of interest. In muscle tissue an absorbed power density of 0.06 Watts/cm² will produce an initial rate of temperature increase of 1° C per minute.

For superficial local tumors microwave heating with external applicators would be sufficient. The field size would be large enough to cover the tumor and normal tissue surrounding it. The applicator usually has sizes of 8 x 8 cm, 10 x 8 cm, 12 x 10 cm and 6 x 12 cm.

For deep-seated tumors below the surface of the skin, microwave local heating with external or interstitial antennae would be possible. Coaxial antennae operating at frequencies of 850 to 1000 Megahertz are applied. Antennae are placed in plastic catheters inserted into tumors similar to the use of iridium wire for brachytherapy.

For tumors adjacent to viscera, such as gastrointestinal tumors (esophagus, rectum) or in gynecology (vagina, cervix, uterus) and genitourinary (prostate, bladder) intracavitary microwave could be used.

Local deep heating with radiofrequency electric fields or with conductive or resistive heating is under development.

2. Thermometry

Temperature measurement of tumor and tissue surrounding it is absolutely necessary to obtain during treatment, because of its critical importance and truly reliable method of thermal treatment verification (recommended accuracy and precision of 0.1° C). Invasive thermometers fall into 5 categories:

a. electrically conducting and
b. minimally conducting and
c. non-conducting or optically conducting probes.

Standard thermistor and thermocouple sensor with metallic leads are conducting probes. For thermistor, the sensor is a semiconductor, which resistance decreases with increasing temperature. For thermocouple the temperature sensor is a bimetal.

Minimally conducting probes are highly resistive thermistor white carbon impregnated plastic shield. Non-conducting optical probes employ sensors composed of Gallium arsenide and mixture of pure earth phosphorus.

CASE STUDIES

In the Department of Radiation Therapy, University of Erlanger-Nürnberg, Federal Republic of Germany, during October 1987 to July 1988 there have been two groups of patients, treated with combined radiation and hyperthermia, using LUND BUCHLER Hyperthermia System, 4 010, 915 Mhz/20 W. The first group consisted of 8 patients, and was treated with radiation combined with interstitial hyperthermia. The 8 patients consist of 4 cases of carcinoma of the floor of the mouth, 3 cases of tongue carcinoma, and 1 case of ewing sarcoma. Two cases with 15 antennae, set the other less than that, but minimal 13 antennae. Two cases received 1 time interstitial hyperthermia and 6 cases received 2 times interstitial hyperthermia with interval at least 1 week. Optimal time for heating ranged between 45 to 65 minutes at 42° C.
The results of these two combined modality treatment approaches are: 7 cases have complete remission (87.5%) and 1 case has partial remission (12.5%). Complication noted in the group with complete remission: 3 cases showed a soft tissue necrosis, and one of them needed a graft.

The second group consisted of 6 patients treated with combined modality, radiation therapy and external (superficial) hyperthermia, using LUND BUCHLER hyperthermia system 40.0 to 915 MHz/20 W. For coupling hot water was used. External hyperthermia was performed both superficially and interstitially inserted into plastic tubes below the surface in the center and margins of the tumor. The heating time ranged between 45 to 65 minutes at 45°C. Five patients had breast cancer recurrence in the chest wall and some others in the supraclavicular region. One case had cancer of the parotid gland. Radiation therapy was applied with electron beam 12 Mev from Mevatron 50 with doses ranging from 35 Gy to 50 Gy. Two cases received 5 series of superficial hyperthermia and 1 case received 10 series of hyperthermia with an interval of one week.

The results of this combined modality treatment are: 4 cases have complete remission (66.6%) and 2 cases have partial remission (33.4%). In the group showing complete remission, 1 case has 6 months following treatment recurrence outside the field. Two cases developed small blisters which healed within days.

![Diagram](image-url)
FIGURE 5. Temperature in the vegetative as recorded by computer. Here in several points of tests inside the tumor, below the tumor and superficial on the skin are measured by thermoelectric sensor, thus curves are displayed on computer screen monitor.

FIGURE 6. - Hypertension treatment log used for recording important data, including power, temperature in tumor, skin, etc.
ABSTRACT

Two groups of mice were treated with combined modality radiation and hyperthermia at the Städtisches Klinik, Universität Erlangen-Nürnberg, Federal Republic of Germany. From October 1967 to July 1988. The first group of 8 patients (4 cases of carcinomas of the floor of the mouth, 3 cases of tongue carcinomas, 1 case of Esophagus carcinoma) was treated with combined radiation and thermal hyperthermia. 7 cases have complete remission (87.5%), whereas 1 case has a partial remission (12.5%). The second group of 6 patients (2 breast cancer recurrences in the chest wall and supravacular region, 1 case with cancer of the parent gland) were treated with combined radiation of electron beams 15 MeV by Siemens Meerbus 20 and superthermal hyperthermia using Luft Bichler hyperthermia system 400 I, 215 MHD/20 W, once a week. 5 cases have complete remission (83.3%) and 1 case has partial remission (16.7%). As background of hyperthermia we also describe the principles of thermotherapy, heat interaction with irradiation, physiologic mechanisms, and effects of hyperthermia on micrometastases of tumors as well as basic principles of physics and instrumentation of hyperthermia.

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